Abstract

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Project Title: Inhibitors of the NS3 Proteinase of West Nile and Dengue Viruses

Abstract: DESCRIPTION (provided by applicant): The purpose of this application is to describe our low risk/high reward, timely and sharply-focused structure-based drug design effort against West Nile virus and Dengue hemorrhagic fever. The target of our drug design effort is the essential processing NS2b-NS3 serine proteinase of flaviviruses, a single proteinase encoded by the viral genome. The presence of the functionally active, mature NS3 proteinase is absolutely essential for the virus life cycle, virus propagation and disease progression. The immediacy and intensity of our effort is directly responsive to the US government's decision that flaviviral infections caused by these viruses are a potential weapon of a bioterrorist. These viruses are categorized by NIAID as Category A-C priority pathogens. There are also hundreds of millions of cases of flaviviridae infections worldwide and, in addition, thousands of cases of West Nile virus in the US. Currently, there are no effective countermeasures against flaviviral infections. Despite the needs of Biodefense and a growing number of naturally-infected patients, there is currently no specific treatment or vaccine to cure or prevent West Nile and Dengue infections. Obviously, there is an urgent need for a potent and safe antiflavivirus therapy. The Burnham Institute team that will implement any research program resulting from this proposal will be drawn from the laboratories of the Infectious and Inflammatory Disease Center, and the Center for Proteolytic Pathways of the Burnham Institute (La Jolla, CA). The team will be lead by Dr. Alex Strongin, PI. Currently, Dr. Strongin is guiding several NIH-funded projects on proteinases including the NIAID-funded proposals "Structure-based Drug Design for Smallpox Therapy" and "Develop effective inhibitors of anthrax lethal factor", and his overarching stewardship will insure program-to-program cost effectiveness and scientific value.

THE SPECIFIC AIMS OF OUR PROJECT ARE: 1. Identify drug-like small molecule inhibitors of the NS3 West Nile virus protease by high throughput screening of chemical libraries. 2. Identify drug-like small molecule inhibitors of the NS3 Dengue virus protease by high throughput screening of chemical libraries. Future plans include optimization the structure of the novel, low-molecular weight, synthetic inhibitors of the West Nile and Dengue virus NS3 proteinase and to validate the selectivity and potency of the selected drug leads in additional in vitro tests and assays. In addition, we will determine, at the atomic resolution level, the structure of the NS3 protease bound to lead antagonists. The foundation for this drug development project is the expertise and experience of the Burnham team in the discovery of novel drugs for infectious and immune diseases and the recent exciting discoveries directly related to this particular project. Vast amount of structure-activity data, which will flow from this project, will facilitate creation of therapeutically important, anti-viral, drugs.

Thesaurus Terms:
High throughput screening, NS3 Proteinase, West Nile Virus, Dengue Virus, Dengue hemorrhagic fever, NS2b-NS3 serine proteinase of flaviviruses, flaviviridae infection, flaviviral infection, small molecule inhibitors of the NS3 West Nile virus, small molecule inhibitors of the NS3 Dengue virus, assay, structure-activity data, anti-viral drug

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